Pediatric Product Development and the FDA: What does the "F" stand for?

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Learning Objectives

- Describe the role FDA plays in the development of products used to treat children
- Briefly review important legislative
- Explain regulatory framework for pediatric product development
- Identify common stumbling blocks and challenges in the process

Pediatric Drug Development General Principles

- Pediatric patients should have access to products that have been appropriately evaluated
- Product development programs should include pediatric studies when pediatric use is anticipated

From FDA guidance to industry titled *E11 - Clinical Investigation of Medicinal Products in the Pediatric Population,* December 2000

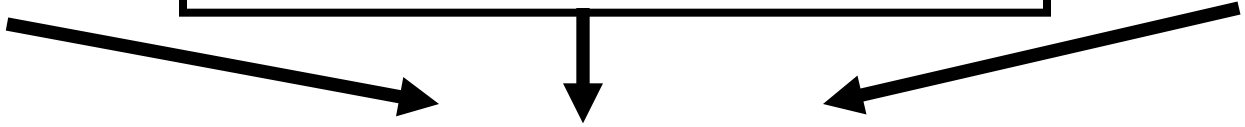
Pediatric Product Development: The Historical Problem

Acknowledged different drug responses, toxicity, and metabolism in adults versus children

Discouraged the study of drugs in children

- Concerns related to ethical issues
- Fears of harming children
- Perceived increased liability of testing drugs in children

Lacked an incentive for drug companies to conduct pediatric trials



Choices for Pediatric Practitioners

- Not treat children with potentially beneficial medications because they are not approved for use in children
- Treat with medications based on adult studies with limited or anecdotal pediatric experience (off-label use)

Pediatric Drug Development

- 1994: Pediatric Labeling Rule
  - Required manufacturers to survey existing pediatric data and to labeling
  - Pediatric Extrapolation "introduced"
- 1997: Food and Drug Administration Modernization Act
  - First incentive program for conducting pediatric studies on drugs
- 1998: Pediatric Rule
  - First requirement for manufacturers to conduct pediatric studies in certain drugs

Pediatric Drug Development Laws

- Best Pharmaceuticals for Children Act (BPCA)
  - Passed by Congress in 2002
  - Section 505A of the Federal Food, Drug , and Cosmetic Act
  - Provides a financial incentive to companies to **voluntarily** conduct pediatric studies
  - FDA and the National Institutes of Health partner to obtain information to support labeling of products used in pediatric patients (Section 409I of the Public Health Service Act)

Pediatric Drug Development Laws

- Pediatric Research Equity Act (PREA)
  - Passed by Congress in 2003
  - Section 505B of the Federal Food, Drug, and Cosmetic Act
  - **Requires** companies to assess safety and effectiveness of certain products in pediatric patients

Goal of PREA and BPCA

PREA  ***BPCA***

Approved Pediatric Labeling

Based on sufficient evidence to support the safe and effective use of medications to treat pediatric patients

Evidentiary Standard for Approval

- For approval, Pediatric products held to same evidentiary standard as products used for adult conditions
- Drugs must:
  - Demonstrate **substantial evidence of effectiveness/clinical benefit** (21CFR 314.50)
  - Clinical benefit:
    - The impact of treatment on how patient feels, functions or survives
    - Improvement or delay in progression of clinically meaningful aspects of the disease

Substantial evidence

- Evidence of effectiveness [PHS Act, 505(d)]
  - Evidence consisting of adequate and well – controlled investigations on the basis of which it could fairly and responsibly be concluded that the drug will have the effect it purports to have under the conditions of use prescribed, recommended, or suggested in the labeling

Adequate and well-controlled study

- Study has been designed well enough so as to be able "to distinguish the effect of a drug from other influences, such as spontaneous change..., placebo effect, or biased observation" (§314.126)

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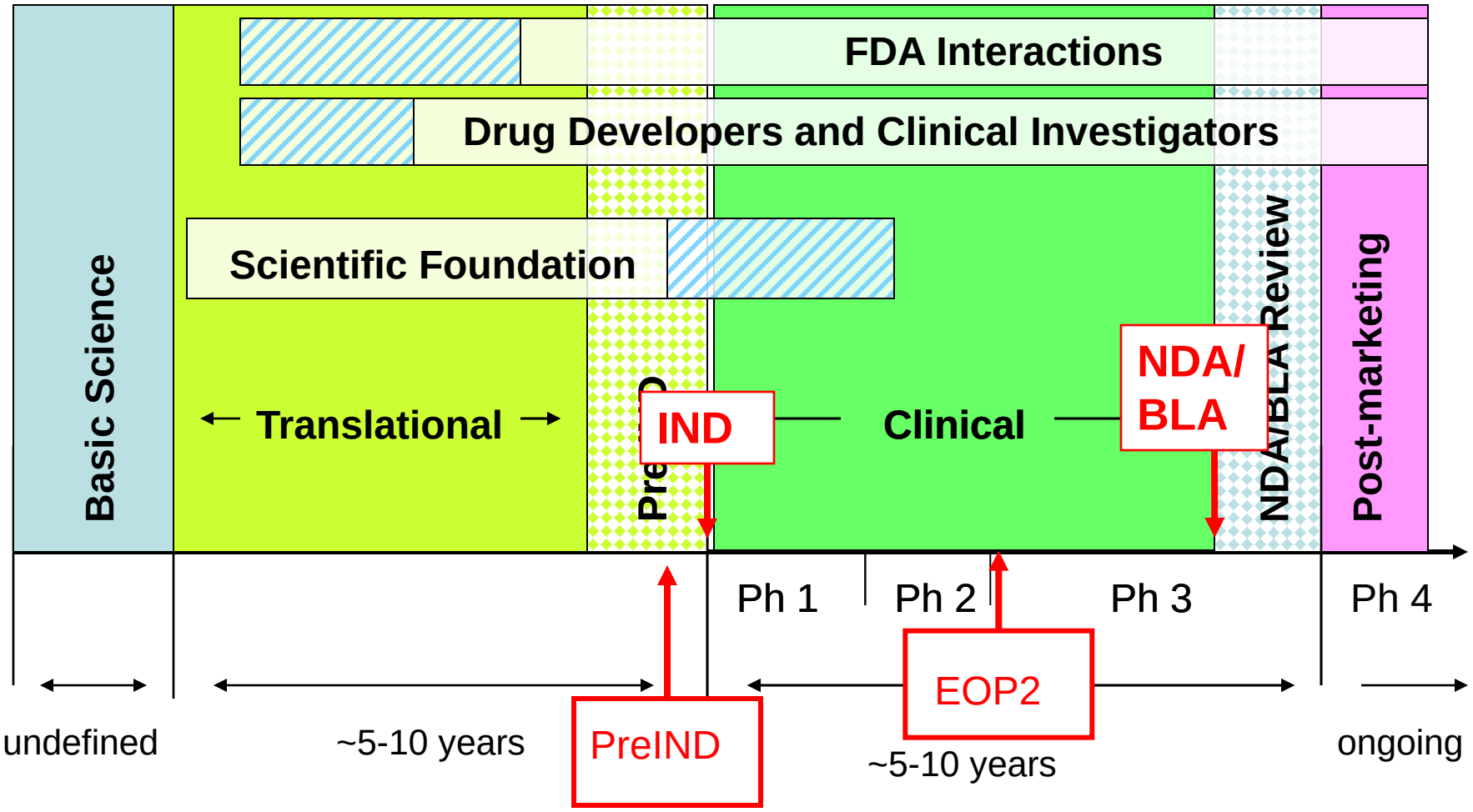
Elements of A & WC Study

- Must incorporate generally accepted scientific principles for clinical trials
- Major elements of the study design:
  1. Clear statement of purpose
  2. Permits a valid comparison with a control
     - Concurrent: placebo, no-treatment, active, dose-comparison
     - Historical
  3. Method of selection of subjects
  4. Method of assigning patients to treatment/control groups
  5. Adequate measures to minimize bias
  6. Methods of assessment of response are well-defined and reliable
  7. Analysis of the results is adequate to assess the effects of the drugs

FDA Oversight

- FDA's primary objectives in overseeing all phases of clinical investigations are:
  - To assure the safety of subjects
  - To assure that quality of scientific evaluation of drugs is adequate to permit an evaluation of the drug's safety and effectiveness
  - To assure that for later phase investigations, the scientific quality of the clinical investigation is adequate to provide data capable of meeting statutory standards for marketing approval (§312.22)

Drug Development Overview



Investigational New Drug (IND) Application

- Generally will contain, at minimum (§312.23)
  - Animal pharmacology and toxicology studies
    - To permit assessment of whether “reasonably safe” for human testing
  - Manufacturing information
    - Product composition, stability
    - Must ensure that the product can be adequately and consistently produced
  - Clinical protocols and investigator information adequate for phase of investigation
- Expected to vary widely depending on many factors
  - Novelty of drug, previous experience, developmental phase, etc.

Common Concerns

- Clinical Hold (§312.42)
  - Subjects would be exposed to an unreasonable and significant risk of illness or injury
  - Insufficient information to assess risks to subjects
    - Lack of characterization of drug/biologic (CMC)
    - Lack of pre/non-clinical data (e.g., animal toxicology)

Common Concerns

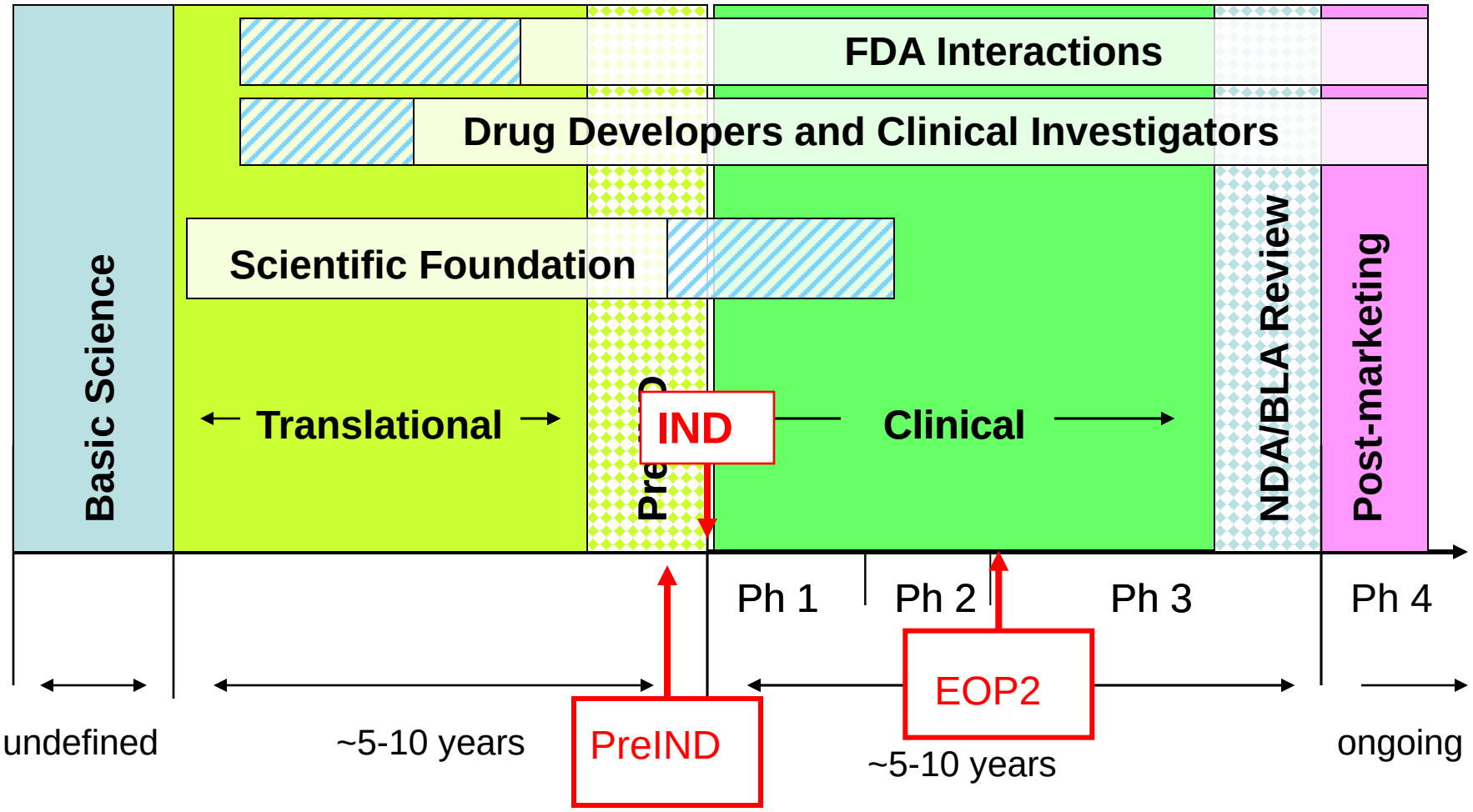
- Animal Toxicology Studies*
- Is the drug safe to administer to study subjects:
  - Identify initial "safe dose" for clinical trials based on safety margin from animal studies
  - Dose-escalation plan and safe stopping dose
  - What organs/systems are at risk?
  - Dose limiting toxicities – what should be monitored in clinical trials? Are toxicities reversible?
  - How will drug be administered – dose, duration, route?
  - Target population (e.g., children, infants)
- Make sure adequate safety support is initiated early and performed properly or can delay clinical program

*Jacobson-Kram D, OND/CDER. Preclinical Safety Testing of Drugs. Presentation to The Israel Chapter of PDA. July 15-16, 2008

FDA Guidance

- Discuss issues with FDA early
  - Entitled to meetings with FDA
  - Early and frequent communication with FDA is essential for successful programs
  - Meet early and often
- Pre-IND meeting
  - Gain advice about specific animal toxicology studies needed
  - Gain advice about any potential chemistry or manufacturing concerns
  - Discuss clinical issues regarding initial clinical studies under the IND

Drug Development Overview



Phase 2: Trial Design Considerations

- Population
  - Age groups, severity of disease, phenotype
- Doses to be studied
  - Dose ranging studies, PK studies, modeling and simulation
- Length of study
  - Length of controlled treatment, longer-term safety extension
- Endpoint(s) selection
- Pediatric Extrapolation

Clinical Endpoints

- Clinically meaningful endpoint
  - A direct measure of how a patient feels, functions or survives
  - Overall survival; Development of end-stage renal disease
- Surrogate Endpoint
  - An endpoint which utilizes a biomarker that is intended to substitute for a clinically meaningful endpoint
  - Change in a surrogate endpoint results in, or is expected to predict clinical benefit (or harm or lack of benefit or harm) based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence
  - A subset of biomarkers may be suitable for use as surrogate endpoints
  - Change in blood pressure; decrease in blood urea nitrogen

Biomarker Definition

- A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- Different sources
  - Serum or plasma
  - Radiographic
  - Tissue
- Not all biomarkers, even clinically useful biomarkers, are suitable for use as surrogate endpoints

Biomarkers in Clinical Research

- Identify a target population for study
  - Patients with a blood phenylalanine level of at least 450 µmol/L for PKU trial
- Refine dose and/or dosing interval
  - Increase in urinary glycosaminoglycan levels in MPS VI trial
- Population is more likely to respond to treatment based on the disease and the mechanism of action of the drug
  - Patients with specific CFTR gene mutations in CF trial
- Does not mean that these biomarkers are acceptable clinical endpoints

Surrogate endpoints

- Validated Surrogate Endpoint
  - An endpoint based on a biomarker for which evidence has established that a drug-induced effect on the surrogate predicts (results in) the desired effect on the clinical outcome
  - Can be used to support regular approval
  - Example: Blood pressure for antihypertensive agents
- Unvalidated Surrogate Endpoint
  - An endpoint based on a biomarker for which it is reasonably likely based on epidemiologic, therapeutic, pathophysiologic or other evidence to predict clinical benefit, or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity
  - Cannot be used to support regular approval
  - Can be used to support “accelerated approval” under 21 CFR314.500
  - Example: Tumor regression in certain types of refractory tumors

Considerations for use of biomarkers as endpoints

- This evidence should include that the biomarker must be
  - reproducible within patients
  - responsive to clinically meaningful changes in disease activity
  - defined with respect to its temporal relationship with disease activity
  - change in expected direction with known effective treatments
  - that the biomarker of interest lies in the causal pathway of the disease.
- Identification of a potential biomarker that could be used as a surrogate marker in phase 3 trials requires
  - Careful and early planning
  - Discussion and concurrence of plans with the review division

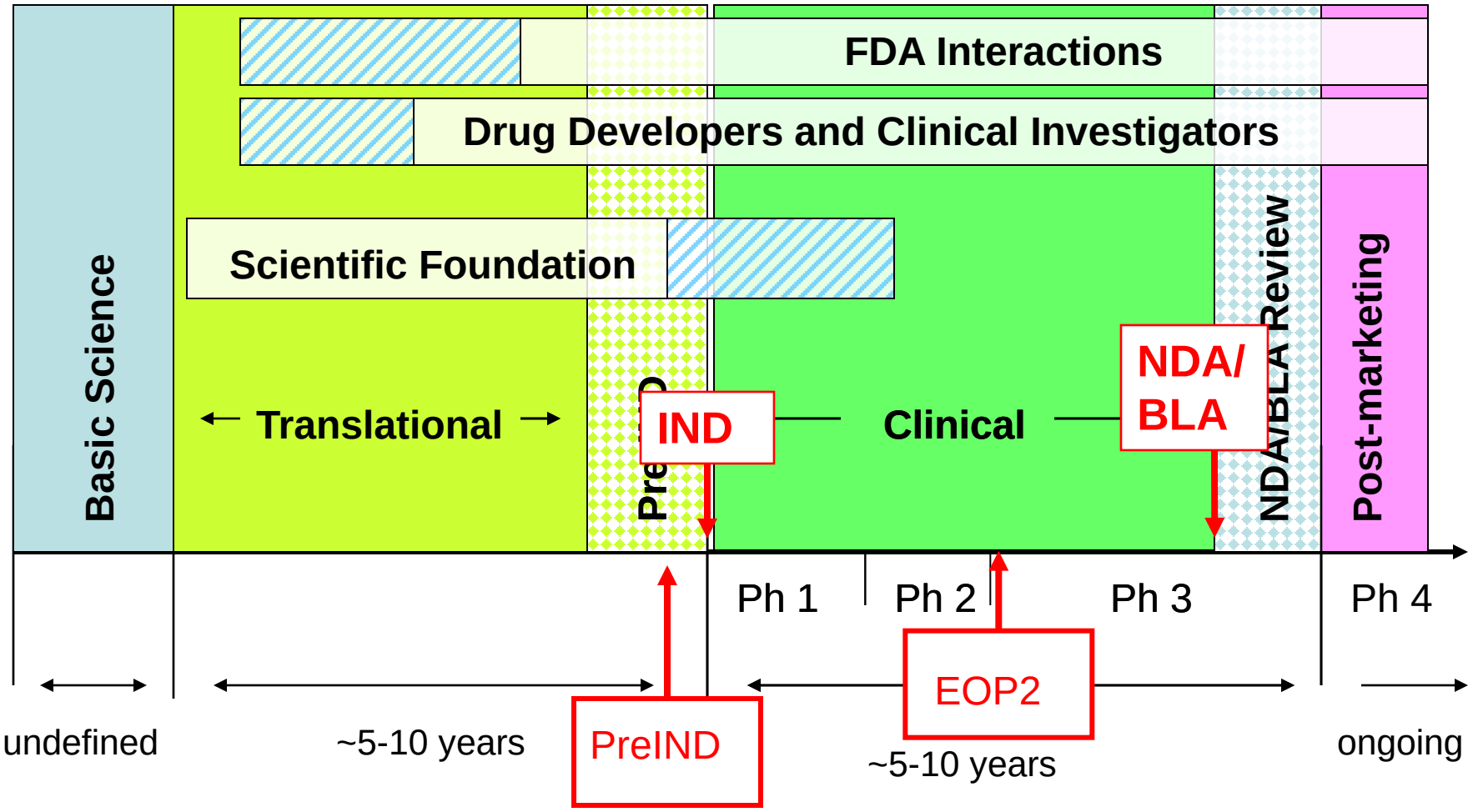
Common Concerns

- Plan/protocol for the investigation is clearly deficient in design to meet its stated objectives
  - Length of study
  - Choice of endpoints
  - Dose selection and dosing regimens
  - Use of pediatric extrapolation
- Appropriate formulation development
- Completion of juvenile toxicity studies, if needed

Addressing Concerns with FDA

- End of Phase (EOP1 and EOP2) meetings
  - Gain advice about potential endpoints for phase 3 study(ies) or use of pediatric extrapolation
  - Gain advice about dose selection dosing issues
  - Gain advice about specific chemistry, nonclinical, and clinical pharmacology studies
- Submission of initial Pediatric Study Plan
  - Document that describes overall plans under PREA to complete pediatric studies

Drug Development Overview



Marketing Applications

- NDA, BLA, or Efficacy Supplement
  - Includes all information to support approval of a product for a specific indication(s)
  - Includes nonclinical studies, clinical trials, chemistry information
- Pediatric Plan
  - PREA required studies, if any, are negotiated
- Pediatric Labeling
  - Indications, Dosage and Administration, Warnings and Precautions, Contraindications, Section 8.4: Pediatric Use Information

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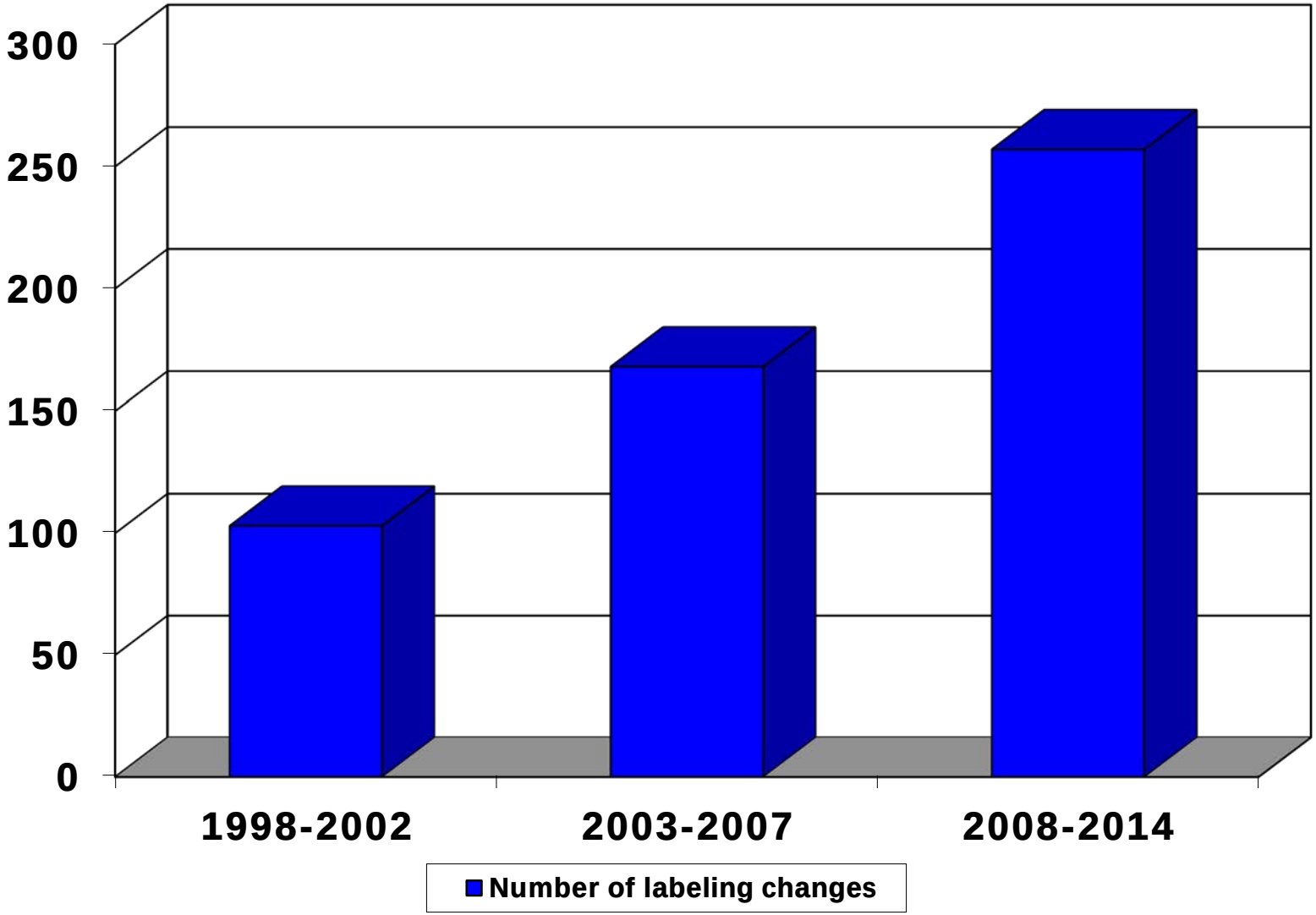
Pediatric Labeling Changes 1998-2014
Total = 528



Conclusions

- Best access for patients to an effective therapy is an approved drug
  - Over 500 labeling changes with pediatric-specific information
- No one right way to do things for pediatric product development
  - Pediatric extrapolation vs. adequate and well-controlled trials
- Design Considerations based on disease, drug/product characteristics, population under study, etc.
- Still need to demonstrate “substantial evidence of effectiveness”
  - Flexibility in how that is achieved…
  - Pediatric extrapolation

Conclusions

- Strong communication with FDA increases chances of a successful outcome
  - Meet early and often (formal meetings)
  - Reach agreement on clinical trial design, endpoints, population for study, length of study, comparators, etc.
- Much work can begin even as adult study is ongoing
  - Map out clinical develop program as early as possible
  - Formulation development
  - Juvenile nonclinical studies, if necessary
- What was reasonable in one situation, may not apply to another

Pediatric Contacts within FDA

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What does the “F” stand for?

- Flexible
- Fair
- Frank
- Foundational
- Familiar
- Facile
- Forward-thinking